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A Single Center Study Comparing the Effects of Laparoscopic Proximal Gastrectomy and Laparoscopic Total Gastrectomy for Siewert types II /III Cancers

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ABSTRACT

Introduction: *In recent years, the incidence of esophageal junction cancer (EGJ) has increased. The management of Siewert type II remains undecided while total gastrectomy with distal esophagectomy is mostly recommended for type III. Data is still lacking from studies assessing proximal and total gastrectomy approaches without thoracotomy as the surgical management of these types of cancer.*

Methods: *Data was retrospectively collected on histopathological characteristics, short-term complications, hemoglobin, total protein, albumin and weight changes. 18 patients with type II, 15 patient type III underwent proximal gastrectomy-Double tract reconstruction (PG-DTR) and 17 patients and 10 patients with type II and III respectively, underwent total gastrectomy-Roux-en y (TG-RY). Patients were followed up every 3 months for one year. The Spitzer-index was used to assess quality of life (QOL) at months 3,6 and 12.*

Results: *There was no statistical significance for operation time, length of hospital stay, blood loss, and change in weight at 6 months after surgery. Changes in hemoglobin, total protein and albumin also failed to show statistical significance (P=0.517, P=0.885 & P=0.8237, respectively). Recurrence was seen in 18.5% and 21.2% of TG and PG group respectively. QOL was significantly better in PG-DTR (P=0.017).*

Conclusions: *This study failed to show any difference for intraoperative and short-term complications between the two procedures. PG-DTR might provide better QOL for patients with types II/III cancer. In addition to D2, Siewert II/III tumors of larger sizes may require extended lymphadenectomy. This study needs further verification with larger cohort, additional parameters, and extended follow up periods.*

KEYWORDS: *Esophagogastric junction, Esophageal cancer, Gastric Cancer, proximal gastrectomy, total gastrectomy*

ABBREVIATIONS

AEGJ: Adenocarcinoma of the Esophagogastric Juntion

Alb: Albumin

CT: Computed Tomography

DTR-Double tract reconstruction

EGJ: Esophagogastric Juction

Hb:Hemoglobin

MRI: Magnetic Resonance Imaging

OS: Overall Survival

PG-Proximal Gastrectomy

PET: Positron Emission Tomography

RY-Roux-en-y

TG: Total Gastrectomy

Tp: Total protein

QOL: Quality of life

INTRODUCTION

The esophagogastric junction (EGJ) can be defined as the area where the stratified squamous mucosa-lined esophagus ends, and the columnar mucosa-lined stomach begins (1). The definition, classification, and management of EGJ has differed among surgeons since, it cannot be singly classified

as just gastric cancer or an esophageal cancer. Siewert et al provided one of the most used classification systems for cancers of the EGJ, which today has provided some guidance on the diagnosis and management of this disease. They classified adenocarcinomas of the esophagogastric junction (AEGJ) into types I, II and III. Siewert type I are classified more as esophageal cancers as they are carcinomas of the distal esophagus, usually arising from an area of intestinal metaplasia like Barrett's esophagus and is 1-5 cm above the EGJ. Siewert type II which is described as the "true" EGJ cancer is located 1cm above and 2 cm below the EGJ and arises from the cardiac epithelium or short segments of intestinal metaplasia. Type III Siewert which is more gastric in origin are sub-cardial gastric carcinomas, 2-5 cm below the EGJ which infiltrates the junction and distal esophagus from below (2). For cancers of the EGJ, surgical management with appropriate lymphadenectomy remain the standard treatment, but in advanced stages and with large tumors, the prognosis remains poor with high recurrence rates. (3–5).The surgical management for especially Siewert type II remains controversial, and the choice of surgical management differs among surgeons. However, many authors have suggested that total gastrectomy with distal esophagectomy might provide better outcomes for patients with Siewert type III cancer (6–8).Most of the data available focuses on the left and right transthoracic, trans thoracoabdominal or transhiatal approaches for managing Siewert type cancers. This has resulted in a lack of data on the trans-abdominal approaches of total gastrectomy (TG) and proximal gastrectomy (PG) without thoracotomy as a method of treatment for these cancers. Hence, this has persuaded and resulted in the formulation of this study to investigate these techniques. In China, Siewert type II and III are usually treated by gastrointestinal surgeons with either PG or TG and appropriate lymphadenectomy, while, Siewert type I cancers are referred to the cardiothoracic department for management. The purpose of this study is to observe the effects of TG versus PG with adequate reconstructive procedures on the length of hospital stay, intraoperative parameters (blood loss, surgical time, intraoperative complications), short term and long term hematological and nutritional effects in addition to, the gastrointestinal quality of life (QOL) for patients with type II and III cancer of the EGJ.

METHODS

Patient Selection

Data on patients demographics, histopathological and surgical characteristics was collected retrospectively from the Tongji Hospital, Wuhan medical data base from January 2019 to January 2021.Patients were selected if they were diagnosed with EGJ cancer Siewert typse II or III with stages I-III according to AJCC/UICC classifications for gastric cancer staging (9–11).Preoperatively patients were diagnosed via upper gastrointestinal endoscopy or endoscopic ultrasound (EUS). Tumor location, tumor depth of invasion, tumor size and biopsy for pathological evaluation were obtained. Computed Tomography (CT)/Magnetic Resonance Imaging (MRI) and Positron Emission Tomography-CT (PET-CT) were used to investigate the thoracoabdominal and pelvic regions for metastatic lesions. Patients with stage IV cancer, patients with unresectable tumors, other malignancies, distant metastasis and any uncontrolled or severe comorbidities with poor general status were excluded from the study. Patients-family consultations were held with surgeons and written consent was obtained before surgery. A total of 33 patients selected underwent PG and 27 underwent TG.

Post-Surgical Short-Term, Long-Term Complications and QOL Assessment

Data for tumor histopathology, operation time, total blood loss, length of hospital stay (calculated from day one post-surgery to the day of discharge), pre-surgical and post-surgical (6 months and 1 year) hemoglobin (hb), total protein (tp), albumin (alb) and weight in kilograms (kg) were retrieved retrospectively. During the first year after surgery patients were followed up every 3 months at the outpatient department where assessment on post-operative complications and gastrointestinal QOL after surgery was performed and data recorded. The Spitzer QOL index questionnaire was used to monitor the QOL of patients at months 3,6 and 12 during the follow up period. Spitzer QOL index is a concise form that is used to assess the QOL of patients with cancer. It assesses patients' activity, daily life functioning, health, social support, and behavior with a score ranging from 0 to 10 (12). The questions are graded from either 0 to 2. A total score of 10 can be obtained after completion, 0 is the worst score and 10 is the best score. The Spitzer QOL index is a validated tool used in many centers and studies around world (13,14). Recurrence and metastasis in patients were monitored as the first date cancer was identification on radiological studies. The site of recurrence and mode of metastasis were also recorded.

Surgical Procedure

Patients selected had to have undergone either laparoscopic TG or laparoscopic PG with D1 or D2 lymph dissection at the discretion of the surgeon and surgical teams. Surgeons made the decision about the best surgical approach taking into consideration tumor size, location, depth of invasion and risk of nodal metastasis. Surgery was performed in accordance with Japanese Gastric Cancer guidelines (15). After PG, double tract reconstruction (PG-DTR) was used to reestablish intestinal continuity. For patients in the TG group Roux-en y (TG-RY) was the reconstructive method utilized. The surgical procedures of PG/TG and DTR and RY are already well documented in literature (16–19). Patients all had R0 resection margins confirmed by histopathological

testing and a minimum of 15 lymph nodes were resected for nodal assessment.

Statistical Analysis

Data was analyzed using the IBM SPSS statistics version 28.0.1.1.0 for Windows. Continuous variables were expressed as percentages or mean (+- Standard Deviation), median and were compared using the Mann Whitney U test. Comparison of categorical variables was done using the Fisher's exact test or Chi Squared test. A P value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

(*Table 1*) summarizes patients demographics and histopathological characteristics based on surgical procedure. A total of 60 patients were included in the study, 55% underwent PG-DTR and 45% TG-RY. 58.3% patients had Siewert type II cancer and 41.6% with type III Siewert. At diagnosis the mean age was 61.5 years and 59.2 years for PG and TG respectively with mostly men affected. These results failed to show statistical significance.

Table 1. Patient demographics and histopathological characteristics by surgical type

Characteristics Total N=60	***PG N= 33 (55%)***	***TG N=27 (45%)***	***t/x^2***	***P-Value***
Sex				
Male	19	16	0.017	0.894
Female	14	11		
Age at diagnosis (mean range)	61.5	59.2	0.043	0.834
Siewert type				
II	18	17	0.432	0.511
III	15	10		
Histopathological Differentiation				
Well	11	8		
Moderately	13	10	0.570	0.752
Poorly	9	9		
Tumor Staging				
I	6	4		
II	11	10	1.358	0.244
III	16	13		
Nodal Status				
N0	8	5		
N1	10	7		0.789
N2	11	9		
N3	4	6		
Histopathology Classification				
Adenocarcinoma	22	19		
Mixed	8	6	0.106	0.948
Unknown	3	2		
Tumor Size				
≦4cm	22	14	1.358	0.244
≧4cm	11	13		

Surgical Outcomes and Short- Term, Long Term Complications

Mean hospital stay was longer for PG-DTR in comparison to TG-RY although the results failed to reach statistical significance (P=0.08). Blood loss was less in the PG-DTR group (78.6+21.2 ml) but no statistical difference was seen between the groups. Length of hospital stay was slightly longer for the PG group (7.8+1.2 ml vs. 8.6+1.3 ml, P=0.84). Short term complications were considered as those which occurred from day 0-30 post operatively. In the TG-DTR group two patient suffered post-operative complication of Cholecystitis which was treated conservatively and another with hemoperitoneum diagnosed via CT scan at day 5 post-surgery. The patient had relaparotomy with 500 ml of clotted blood extracted but no active bleeding

was identified. In the PG-DTR one patient experienced fever secondary to infection of the surgical site, the patient was treated successfully with debridement and intravenous antibiotics.

The mortality rate post-operative mortality rate was at 0% and no patient died within the year follow up period. At about of day 7 post operatively patients underwent fluoroscopy with oral contrast medium performed to observe for appropriate shunting of contrast into the remnant stomach and for sign of anastomotic leak. The results showed no anastomotic leak and patients had successful shunting of contrast into the remnant stomach. This data is summarized in (*Table 2*).

Table 2. Surgical and Post-surgical parameters based on surgical resection

Parameters	***TG***	***PG***	***t/x2***	***P-value***
Weight before surgery (kg)	67	64	-	0.900
Weight at 6 months post-surgery (kg)	61	55	-	0.400
Surgery time (min)	200.5±12.1	236.3±10.6	2.966	0.085
Blood loss (ml)	98.3±6.9	78.6±21.2	2.194	0.139
Length of hospital stay (d)	7.8±1.2	8.6±1.3	0.039	0.843

TG=Total Gastrectomy, PG=Proximal Gastrectomy. Length of hospital stay was calculated from day 1 post operation to the date of discharge.

Nutrition/Weight/Hb

Pre-operative values for hb were similar between the surgical types and although it did not reach statistical significance, at 6 months and 1-year post surgery hb decrease was greater in TG-RY in comparison to PG-DTR. There was also no statistical difference between the two groups before and after surgery for tp and alb. Weight change was also similar between the groups at 6 months post operation with no statistical significance (P=0.400). Refer to (*Table 3*).

Table 3. Hematological and nutritional parameters of before and after surgergical procedures

Parameters	***Hb (g/L)***			***Tp (g/L)***			***Alb (g/L)***		
Group	Pre-op	6 months	1 year	Pre -Op	6 months	1 year	Pre-op	6 months	1 year
TG	132.1±7.2	126.3±5.6	123.5±8.4	68.1±5.7	62.4±4.4	61.9±8.3	40.9±4.9	37.1±5.2	35.4±6.8
PG	132.6±5.6	131.9±7.1	133±9.9	69.2±5.2	65.3±4.5	63.5±7.3	41.3±4.2	39.2±6.2	37.3±5.6
t/X2	0.001	0.122	0.420	0.009	0.066	0.020	0.578	0.122	0.049
P	0.976	0.728	0.517	0.925	0.798	0.886	0.810	0.728	0.824

Hb=hemoglobin, Tp,=total protein, Alb= albumin, PG=Proximal Gastrectomy, TG=Total Gastrectomy

Long-term complications and QOL

Long-term post-operative complications to include reflux esophagitis, dumping syndrome, diarrhea, anastomotic stenosis, and abdominal ascites were recorded for the patients. The findings are summarized in (*Table 4*). Reflux esophagitis was similar between the groups (PG=12%, TG=11%). Within the first year 9% of patients in the PG experienced anastomotic stenosis in comparison to 0% in TG. 7% and 3% of patients from the TG and PG groups respectively experienced dumping syndrome, but the results failed to show statistical significance.

Table 4. Surgical complications at 6 months post-surgery

	Patient total	***Reflux Esophagitis***	***Dumping Syndrome***	***Anastomotic Stenosis***	***Abdominal Ascites***
PG	33	4	1	3	0
TG	27	3	2	0	1

Post-surgical evaluation based on on upper gastrointestinal endoscopy and CT-scan findings

(*Table 5*) represents the assessment on the gastrointestinal QOL during the first year after surgery. TG (78%) group suffered significantly higher rates of reflux symptoms, which showed statistical significance P=0.001. QOL using Spitzer method was obtained at months 3, 6 and 12 for patients of both groups. The QOL index increased from 3 months of post operation to last follow up in PG group. In the TG- group there was a slight decrease at month 6 however, it was not significant and improved at month 12. However, QOL was significantly better in the PG group, P=0.017. See (*Fig 1*).

Table 5. Post-surgical gastrointestinal symptoms

Symptoms	*PG (N=33)*	*TG (N=27)*	*P-value*
Frequent abdominal pain	2	3	0.655
Reflux Symptoms	4	21	0.001
Frequent Diarrhea	0	1	0.314
Constipation	3	2	0.658
Indigestion	4	3	0.705
Nausea and vomiting	1	2	0.564

PG=Proximal Gastrectomy, TG=Total Gastrectomy

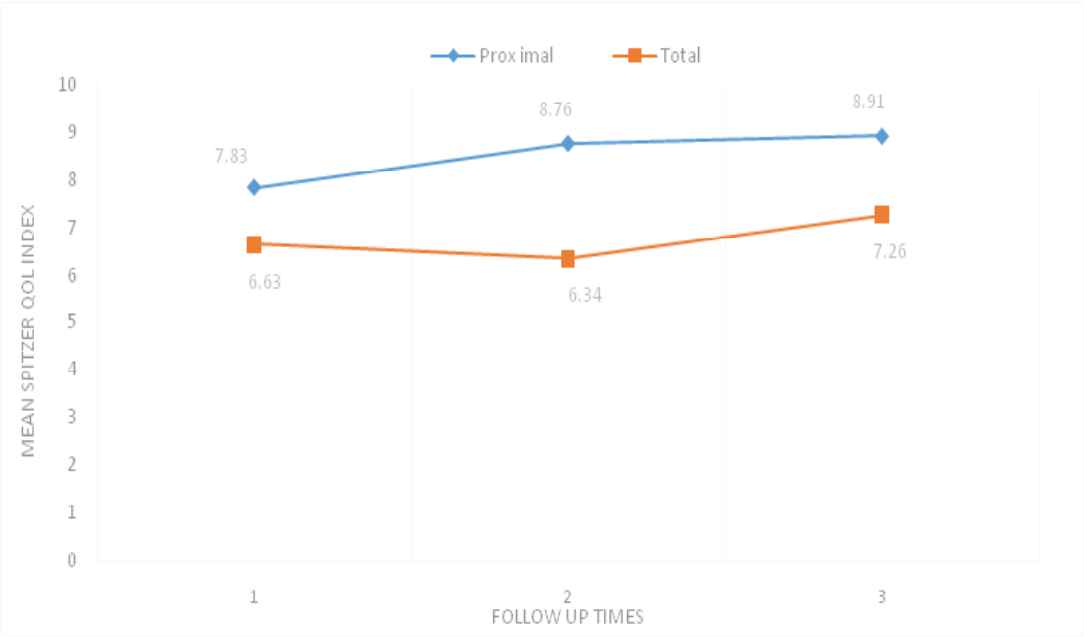

Figure 1. Spitzer QOL-index score by surgical type at months 3,6 and 12, blue line=proximal gastrectomy, orange line=total gastrectomy

Recurrence

During the follow up period 18.5% (n=5) and 21.2% (n=7) in the TG and PG groups respectively had recurrence. The median in months of recurrence for the TG group was 12 months and 6 months in patients who had PG. In the PG group 5 patients (71.4%) were Siewert type III , 2 patients (28.6%) Siewert type II. For the TG group with recurrence 2 patients (40%) had type II Siewert and 3 patients (60%) with type III Siewert. From the analysis the mode of recurrence was predominantly hematogenous to the liver and lungs. Most of the patients with recurrence had stage III tumor, with a total of 7 patients with recurrence having tumors ≥4cm in diameter.

DISCUSSION

Many authors agree that Siewert I should be treated as an esophageal cancer and that type III be treated as a gastric cancer. Nonetheless, the surgical management for Siewert type II remains undecided. This study was constructed to add to the current debate and provide insight into the possible best procedure for Siewert type II or III cancers, and if they can be treated as gastric cancers. At our institution and many others, type II and III Siewert are treated with either PG or TG followed by an adequate reconstructive procedure (29). The problem is that these techniques are not well documented, and studies are lacking.

For optimal surgical management of EGJ cancers it has been established that adequate lymph node and tumor margin resection needs to be carried out (30). As of late, PG for the management of proximal gastric cancer has become popular among surgeons. Multiple studies have indicated that for cancers of the proximal gastric region, TG is not necessary since, the effects of PG are comparable or even more favorable than TG (31–33). However, the incidence of esophageal reflux associated with PG after esophagogastrostomy poses a challenge; and reconstructive procedures reducing the risk of such complications should be utilized. Consequently, techniques like DTR, jejunal interposition, jejunal pouch interposition, double flap and even improvements to the original esophagogastrostomy technique have been adopted to curb the issues of esophageal reflux, anastomosis stricture and leak after surgery(34–36). DTR has also shown promising

results in the improving these symptoms in patients after PG (37,38).

This study showed that with there was no statistical significance for operation time, intraoperative blood loss and length of hospital stay between PG-DTR and TG-RY. These results are supported by studies from Sugiyama et al, Kim et al, and Aburatani et al in their research (19,39,40). Jung et al and Park et al studies in contrast, showed statistical significance of longer operation time for TG in comparison to PG (34,41). Surgical times generally differ between surgeons and institutions, the differences may be attributed to several factors including but not limited to surgical skill, complexity of the procedures, intraoperative complications, and technical mishaps among many other factors.

Post-operative nutritional outcomes between the two procedures did not show statistical significance. These findings correlate with results reported in Cho et al and Kim et al studies (40,42) . In contrast to this study which showed no statistical difference in change of weight between the two procedures at 6 months post-surgery, Sugiyama et al showed statistically significant difference for body weight at 6 months post operation of -14% for TG and -5% for PG (39).

Previous studies have indicated that in Siewert type II and III nodal metastasis mostly involves abdominal nodes and smaller percentages are seen for the lower mediastinum(30,43,44). Other studies disagree and suggest lymph involvement of EGJ cancers are like those of distal esophageal cancer or have significant mediastinal involvement (4,45). Hasegawa et al stated that the appropriate lymphatic resection of Siewert II and III should be D2 lymphadenectomy and the management of these cancers should follow those of gastric cancer (46). Kneuterz et al also reported from their study comparing transthoracic esophagectomy and gastrectomy for EGJ cancers that extended abdominal lymphadenectomy could improve OS(28). This brings into question the choice or need for thoracic or thoracoabdominal approaches in the management of (especially early) EGJ cancers without confirmation of mediastinal nodal metastasis. Kauppila et al showed that TG vs oesophagectomy for Siewert type II or III did not differ in 5-year overall survival, number of lymph nodes retried and radical resection margin. Additionally, because of the complications associated to thoracotomy, gastrectomy might be a better choice (47) . Goto et al suggested that based on lymph retrieval, PG could be a suitable treatment for Siewert type II and TG would be the optimal treatment for Siewert type III (26). Hosokawa et al reported that mediastinal dissection alone of positive nodes in AEGJ seemingly does not improve OS and in patients with suspicion of this perioperative chemotherapy might be beneficial (48).

Many surgeons fear that with gastrectomy inadequate resection margins may not be attainable. Past studies have recommended that optimal resection margin ranging from 4-6cm is required. In their study Ito et al reported that to achieve R0 resection a margin 4cm is needed for T1~T2 tumors, achievable with extended gastrectomy via transhiatal approach. However, 6cm margin is required in stages II-III and can be best achieved by extended gastrectomy with thoracotomy and esophagectomy(22). Another study reported that for Siewert type II positive resection margin was higher in gastrectomy compared to esophagectomy, but in their study patients were treated with neoadjuvant or preoperative chemotherapy before resection(4). Zhu et al conducted an analysis on PG and TG for the treatment of Siewert type II. They reported the excision range in PG might be adequate for Siewert type II AEGJ, since there was no significant difference in survival for the two surgical groups (29) . Available data is not adequate to conclusively decide which one results in better R0 margins and as such only recommendations have been made.

Wang et al performed a study similar to this one for patients with proximal gastric cancer inclusive of some Siewert II and III cases, although they did not give the percentage included. They reported similar findings for intraoperative and short-term complications. However, in their study they included vitamin B_{12} pre-surgery and post-surgery values which we did not, and their staging was restricted to stages cTI-II(49). This study, however, was inclusive of stages pTI-TIII and QOL assessment. This study was able to show a better gastrointestinal QOL for patients who had PG-DTR in comparison to those who had TG-RY. Majority of the patients in the TG group suffered from reflux symptoms and many were partially dependent on others after the surgery. The better QOL in patients with DTR might be attributed to the presence of the remnant stomach which contributes to the maintenance of vitamin B_{12} and maintains secretion of gastric juices to foster the normal cascade of digestion and absorption of nutrition by food passing through the duodenum.

Data on the recurrence of AEGJ is limited however, a study indicated that there was no difference in recurrence rate between the three types of Siewert. Further, they found that hematogenous recurrence was the most common for type II Siewert, while peritoneal was most common for type III with most occurring within 12 months after surgery. In correlation with this study most of their hematogenous recurrence for type II/III also occurred in the liver (48). Studies have indicated that recurrence rate and OS for PG-DTR and TG-REY in proximal gastric cancer treatment does not differ greatly (37,50,51). Recurrence in this study occurred in 58.3% of patients with tumors larger than 4 cm. These results might be explained by possible higher esophageal and lymph node invasion by tumors of these sizes as proposed by Hoshino et al (52) . They reported that in EGJ cancer with tumors ≥ 4cm extended lymphadenectomy to the upper mediastinum might be required to improve OS. This finding requires further validation.

There were several limitations in this study. Firstly, the study was carried out at a single institution with a small study population. Secondly, we did not include several nutritional parameters like vitamin B_{12} or monitoring of skeletal muscle mass, diet intake etc. in this study. Thirdly, our study did not monitor the longer-term effects of about 2 to 3 years and QOL of patients. The study follow up was not long enough to observe5-year OS, disease free progression and failed to show which factors could affect patient survival. Additionally, we included patients with R0 margins but did not include lengths of resection margins by measurements. This could assist in the determination of a suitable length of margin resection required to improve survival and recurrence free rates of patients with Siewert type II/III who undergo PG/TG.

CONCLUSION

This study failed to show any difference for intraoperative and short-term complications and outcomes between the two procedures. PG - DTR is safe and might provide better gastrointestinal QOL for patients with Siewert type II/III cancer depending on the size and invasion of the tumor. This study needs further verification with a larger cohort, additional parameters, and extended follow up periods.

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